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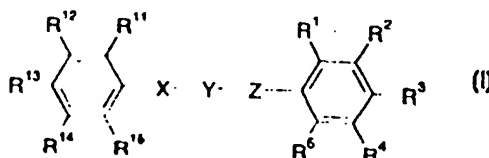
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PHENYL DERIVATIVES CONTAINING AN ACIDIC GROUP. THEIR PREPARATION AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

The present invention relates to phenyl derivatives which are valuable blockers of chloride channels and as such useful for the treatment of sickle cell anaemia, brain oedema following ischaemia or tumours, diarrhoea, hypertension (diuretic) and for the reduction of the intraocular pressure for the treatment of disorders such as glaucoma. The compounds of the invention may also be useful in the treatment of allergic or inflammatory conditions and for the promotion of wound healing.

Background

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of skeletal and smooth muscle cells. Blockers of chloride channels are known to be useful in the treatment of brain oedema following ischaemia or tumours, diarrhoea, hypertension (diuretic) and for the reduction of the intraocular pressure in disorders such as glaucoma.

Sickle cell anaemia and the existence of sickle haemoglobin was the first genetic disease to be understood at the molecular level. The genetic defect underlying sickle cell anaemia causes the substitution of a single amino acid resulting in a mutant haemoglobin, sickle haemoglobin.

The physical manifestations of sickle cell disease is anaemia and painful ischaemic crises due to occlusion of the microcirculation by deformed erythrocytes (sickle cells). The primary cause of sickle erythrocyte deformation and distortion (or sickling) is a reversible polymerisation and gelation of sickle haemoglobin induced at the low oxygen tensions prevalent in metabolically active tissues. Sickle cells are also characterised by an enhanced cation permeability, resulting in cation depletion and cellular dehydration. Since the delay time for the polymerisation has been described as an extremely steep function of the sickle haemoglobin concentration itself, any decrease in cell volume will greatly increase the probability of sickling and thereby of vessel occlusion. Compounds which blocks the deoxygenation induced salt and volume (water) loss may delay the sickling process enough to avoid occlusion upon the passage of the sickle erythrocyte through metabolically active tissue. It has been estimated that a delay time of only 10 sec may suffice.

Several membrane ion channels and transporters present in normal erythrocytes has been suggested to participate in the altered membrane permeabilities of sickle cells. The favoured hypothesis has been stimulation of the Ca^{2+} -activated K^{+} -channel and several blockers of this channel has been suggested as therapeutic agents for the treatment of sickle-cell anaemia (Effects of Cetiedil on Monovalent Cation Permeability in the Erythrocyte: An explanation for the Efficacy of Cetiedil in the treatment of Sickle Cell Anaemia, Berkowitz, L. R., Orringer, E. P., Blood cells, (283-288 (1982) and US patent No. 5.273.992).

Since, K^{+} efflux through a K-channel must be followed by an equal efflux of Cl^{-} to maintain electroneutrality, blockade of erythrocyte chloride channels are predicted to be as effective as blocking the K-channels itself. An advantage to the use of chloride channel blockers is that salt loss which may occur due to activation of unknown K-channel types will indirectly be blocked too.

The compounds of the present invention are valuable blockers of chloride channels as determined by concomitant measurements of conductive netfluxes of chloride and membrane potentials in suspensions of erythrocytes, and the compounds are therefore predicted to be useful for the treatment of ailments responsive to the blockade of chloride channels, including sickle cell anaemia.

The use of blockers of chloride channels for the treatment of sickle-cell anaemia form a new therapeutic approach.

Several chloride channel blockers and the use thereof have already been described in the technical literature:

Pflügers Arch (1986), 407 (suppl. 2), pages 128-141 describe several compounds with chloride channel blocking activity. A very potent compound described herein is 5-nitro-2-(3-phenylpropylamino)benzoic acid. The reference do not disclose the use of chloride channel blockers for the treatment of sickle cell anaemia.

US patent No. 4.889.612 describes Calixarene derivatives and their use as chloride channel blockers.

US patent No. 4,994,493 describes certain 5-nitrobenzoic acid derivatives and their use in the treatment of cerebral oedema.

WO 96/16647 describes the use of chloride channel blockers for the reduction of the intraocular pressure and specifically the use of chloride channel blockers for the treatment of glaucoma.

Objects of the Invention

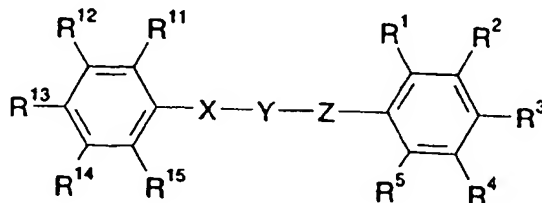
It is an object of the present invention to provide a series of phenyl derivatives carrying an acidic group and pharmaceutically acceptable salts thereof which are useful in the treatment of disorders or diseases responsive to the blockade of chloride channels.

Still another object of the present invention is to provide a method of treating disorders or diseases responsive to the blockade of chloride channels, such as for example brain oedema following ischaemia or tumours, diarrhoea, hypertension (diuretic), glaucoma and in particular sickle-cell anaemia. A further object of the present invention is to provide a method for the treatment of allergic or inflammatory conditions and for the promotion of wound healing.

Summary of the Invention

The invention then comprises, inter alia, alone or in combination:

A compound having the formula



or a pharmaceutically acceptable salt thereof

wherein

one of R¹, R² and R³ is a non-cyclic acidic group having a pK_a value below 8 or a group which is in vivo convertible to such a group;

R^4 , R^5 and the other two of the substituents R^1 , R^2 and R^3 are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl and heteroaryl groups may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or R^3 and R^4 or R^4 and R^5 together form a fused 4 to 7 membered carboxylic ring which may be unsaturated, or partially or fully saturated, while the other substituents R^1 , R^2 , R^3 , R^4 and R^5 is as defined above;

Y is -CO-, -CS-, -SO₂-, or -C(=N-R⁸)-, wherein R⁸ is hydrogen, alkyl, or cyano;

X is -NH-, -CH₂-NH-, or -SO₂-NH-;

Z is NR⁶, O, -CH=CH-, -C≡C-, -N=CH-, or -CH=N-; wherein R⁶ is hydrogen, or alkyl;

R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; -NHSO₂-R⁷, -COOR⁷, -SO₂N(R⁷)₂, -SO₂OR⁷ and -CO-R⁷, wherein R⁷ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl or aralkyl; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl and heteroaryl groups may be substituted one or more times with substituents selected from alkyl, cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R^{11} and R^{12} , R^{12} and R^{13} , R^{13} and R^{14} or R^{14} and R^{15} together form a fused 4 to 7 membered carboxylic ring which may be unsaturated, or partially or fully saturated, while the other substituents R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above;

a compound as above wherein one of R^1 , R^2 and R^3 is NH₂,

-COOR⁹, -CH₂COOR⁹, -CONH₂, -NHSO₂-R⁹, -SO₂N(R⁹)₂, -SO₂OR⁹, -PO₃H₂,

-PO₃RH, -PO₂NH₂, -CONHOH, -CONHCN, -CONH₂SO₂R⁹ and -CONHNH₂, wherein R⁹ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl or aralkyl, and the other of R^1 , R^2 and R^3 is as defined above;

a pharmaceutical composition comprising a therapeutically effective amount of a compound as above or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier or diluent;

the use of a compound as above for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels;

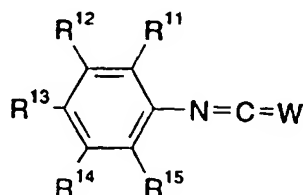
the use of a compound as above for the preparation of a medicament for the treatment of sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic), glaucoma, allergic or inflammatory conditions and ulcers;

a method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to a living animal body in need thereof a therapeutically effective amount of a compound as above;

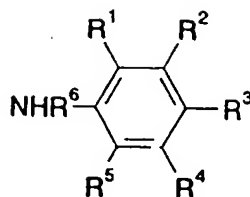
a method for the treatment of a disorder or disease of a living animal body which disorder or disease is sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic), glaucoma, allergic or inflammatory conditions and ulcers comprising administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as above;

a method for the preparation of a compound as above, comprising:

a) reacting a compound having the formula

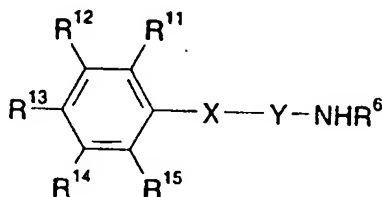


wherein W is O, or S and R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above, with a compound having the formula

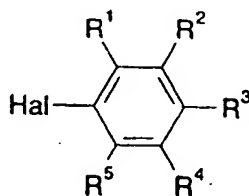


wherein R¹, R², R³, R⁴, R⁵ and R⁶ is as defined above, or

b) reacting a compound having the formula



wherein X, Y, R⁶, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above, with a compound having the formula



wherein Hal is halogen and R¹, R², R³, R⁴ and R⁵ is as defined above,

whereafter the compound obtained is optionally converted to another compound of the invention and/or a pharmaceutically acceptable salt thereof is formed using conventional methods; and

the use of blockers of chloride channels of erythrocytes for the treatment of sickle cell anaemia.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulfate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate. Such salts are formed by procedures well known in the art.

Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Halogen is fluorine, chlorine, bromine or iodine.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Cycloalkyl means cyclic alkyl of three to seven carbon atoms, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Alkenyl means a group of from two to six carbon atoms, including at least one double bond, for example, but not limited to ethenyl, 1,2- or 2,3-propenyl, 1,2-, 2,3-, or 3,4-butenyl.

Alkynyl means a group of from two to six carbon atoms, including at least one triple bond, for example, but not limited to ethynyl, 1,2-, 2,3-propynyl, 1,2-, 2,3- or 3,4-butyne.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Amino is NH_2 or NH-alkyl or N-(alkyl)₂, wherein alkyl is as defined above.

A non-cyclic acidic group having a pKa below 8 or a group which is in vivo convertible to such group include groups such as NH_2 , $-\text{COOR}^9$, $-\text{CH}_2\text{COOR}^9$, $-\text{CONH}_2$, $-\text{NHSO}_2\text{R}^9$, $-\text{SO}_2\text{N(R}^9)_2$, $-\text{SO}_2\text{OR}^9$, $-\text{PO}_3\text{H}_2$, $-\text{PO}_3\text{RH}$, $-\text{PO}_2\text{NH}_2$, $-\text{CONHOH}$, $-\text{CONHCN}$, $-\text{CONH}_2\text{SO}_2\text{R}^9$ and $-\text{CONHNH}_2$, wherein R^9 is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl or aralkyl.

Heteroaryl is a 5- or 6-membered heterocyclic monocyclic group. Such a monocyclic heteroaryl group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl.

Aryl means an aromatic group such as phenyl or naphthyl.

Aralkyl means arylalkyl wherein alkyl and aryl is as defined above, meaning for example benzyl, or phenethyl.

I.p. means intraperitoneally, which is a well known route of administration.

P.o. means peroral, which is a well known route of administration.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

It will be appreciated by those skilled in the art that the compounds of the present invention contain several chiral centres and that such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Some of the compounds of the present invention exist in (+) and (-) forms as well as in racemic forms. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolution of optical isomers, known to those skilled in the art may be used, and will be apparent to the average worker skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

The compounds of the invention may be prepared in numerous ways. The compounds of the invention and their pharmaceutically acceptable derivatives may thus be prepared by any method known in the art for the preparation of compounds of analogous structure, and as shown in the representative examples which follow.

Biology

The compounds of the present invention are potent blockers of chloride channels in normal as well as sickle cell erythrocytes. The ability of the compounds to block the erythrocyte chloride channels could not be demonstrated by classical electrophysiological measurements such as patch clamping, since the channel unit conductance is below the detection limit of these techniques.

All dose-response experiments were therefore performed by concomitant measurements of conductive netfluxes of Cl^- (J_{Cl}) and membrane potentials (V_m) in suspensions of erythrocytes (Bennekou, P. and Christophersen, P. (1986), Flux ratio of Valinomycin - Mediated K^+ Fluxes across the Human Red Cell Membrane in the presence of the Protonophore CCCP. *J. Membrane Biol.* 93, 221-227.). The membrane Cl^- -conductances were calculated by the following equation (Hodgkin, A. L. and Huxley, A.F. (1952) The components of membrane conductance in the giant axon of *Ioligo*. *J. Physiol. Lond.* 116, 449-472):

$$G_{\text{Cl}} = \frac{F \cdot J_{\text{Cl}}}{(V_m - E_{\text{Cl}})}$$

where F is the Faraday constant and E_{Cl} is the Nernst potential for the Cl^- -ion. Administration of N-(3-Trifluoromethylphenyl)-N'-(2-carboxyphenyl) urea to a suspension of normal erythrocytes blocked G_{Cl} more than 95 % with an IC_{50} -value of $0.6 \mu\text{M}$. The compound equipotently blocked G_{Cl} from oxygenated as well as deoxygenated homozygoteous sickle cell erythrocytes.

Experimentally induced cell volume losses were measured as changes in the relative volume of packed cells. Inducing a massive water and salt loss (KCl) by addition the K^+ -ionophore valinomycin to the suspension for 5 min reduced the cell volume by 26 %. N-(3-Trifluoromethylphenyl)-N'-(2-carboxyphenyl) urea dose-dependently (IC_{50} -value of $1.2 \mu\text{M}$) reduced the volume loss to 7 %.

Deoxygenation induced permeability increases of sickle cells were estimated by measuring the extracellular K^+ -concentration vs time. Normal erythrocytes exhibited very small K^+ -fluxes, which was insensitive to deoxygenation and insensitive to $10 \mu\text{M}$ N-(3-Trifluoromethylphenyl)-N'-(2-carboxyphenyl) urea. The K^+ flux from oxygenated sickle erythrocytes was 2-3 times higher than from normal erythrocytes and these fluxes was accelerated 4 - 8 times upon deoxygenation. In presence of N-(3-Trifluoromethylphenyl)-N'-(2-carboxyphenyl) urea ($10 \mu\text{M}$) the basal K^+ -flux from sickle erythrocytes was normalised and the deoxygenation induced flux component were nearly abolished.

N-(3-Trifluoromethylphenyl)-N'-(2-carboxyphenyl) urea was non-toxic to mice at concentrations up to 150 mg/kg i.p. and i.v.

Pharmaceutical compositions

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptically isolating sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Methods of treating

The compounds of the present invention are, due to their potent chloride channel blocking activity, useful in the treatment of sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhoea, and hypertension (diuretic) as well as other disorders responsive to the blockade of chloride channels. The compounds of the invention may also be useful in the treatment of allergic and inflammatory conditions, for the promotion of wound healing or the treatment of ulcers. The compounds of this invention may accordingly be administered to a living animal body, including a human, in need of treatment, alleviation, or elimination of an indication associated with or responsive to chloride channel blocking activity. This includes especially sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhoea, and hypertension (diuretic).

Suitable dosage range are 0.1-500 milligrams daily, and especially 10-70 milligrams daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject

involved, and further the preference and experience of the physician or veterinarian in charge.

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

Example 1**3'-Trifluoromethylphenyl-2-carboxyphenyl urea**

3'-Trifluoromethylphenyl isocyanate (1.87g, 10 mmol) and 2-aminobenzoic acid (1.37g, 10 mmol) were in toluene (50 mL) until the 2-aminobenzoic acid had been consumed. After cooling to room temperature the product was filtered off. M.p. 171-172 °C.

The following compounds were prepared analogously:

- 3'-Trifluoromethylphenyl-3-carboxyphenyl urea. M.p. 183-185 °C.
- 2'-Methoxy-5'-chlorophenyl-3-carboxyphenyl urea.
- 3'-Trifluoromethylphenyl-2-carboxy-5-nitrophenyl urea. M.p. 206-207 °C.
- 3'-Trifluoromethylphenyl-5-chloro-2-nitrophenyl urea. (intermediate)
- 3'-Trifluoromethylphenyl-2-carboxy-4-methylphenyl urea. M.p. 183-184 °C.
- 3'-Trifluoromethylphenyl-4-bromo-2-carboxyphenyl urea. M.p. 199-200 °C.
- 3'-Trifluoromethylphenyl-3-carbamoylphenyl urea. M.p. 205-206 °C.
- 3'-Trifluoromethylphenyl-3-sulfamoylphenyl urea. M.p. 184-185 °C.
- 3'-Trifluoromethylphenyl-5-chloro-2-phenylsulfonamidocarbonylphenyl urea. M.p. 270-300 °C (dec.)
- 3'-Trifluoromethylphenyl-2-methylsulfonamidocarbonylphenyl urea.
- 3'-Trifluoromethylphenyl-6-methyl-2-carboxyphenyl urea. M.p. 166 °C.
- 3'-Trifluoromethylphenyl-3-methyl-2-carboxyphenyl urea. M.p. 181-182 °C.
- 3'-Trifluoromethylphenyl-4-hydroxy-2-carboxyphenyl urea. M.p. 166-167 °C.
- 4'-Nitrophenyl-2-carboxyphenyl urea. M.p. 203-204 °C.
- 3'-Trifluoromethylphenyl-2-carboxymethylphenyl urea. M.p. 182-183°C.
- 3'-Trifluoromethylphenyl-2-sulfophenyl urea. M.p. 182-183°C.
- 3'-Trifluoromethylphenyl-2-carboxyphenyl thiourea. M.p. 210-220°C.
- 3'-Trifluoromethylphenyl-2-carboxy-5-trifluoromethylphenyl urea. M.p. 179 °C.
- 3'-Trifluoromethylphenyl-4,5-dimethoxy-2-carboxyphenyl urea. M.p. 198-199 °C.
- 3'-carboxyphenyl-2-hydroxy-5-chlorophenyl urea. M.p. 216 °C.
- 3'-carbamoylphenyl-2-hydroxy-5-chlorophenyl urea. M.p. 203-204°C.
- 3'-Trifluoromethylphenyl-2-hydroxy-4-nitro-5-carboxyphenyl urea. M.p. 201-203 °C.

Example 2
(intermediate)

2-Chloro-5-hydroxybenzoic acid

5-Amino-2-chlorobenzoic acid (85%, 10g, 49.7 mmol) was suspended in diluted sulphuric acid (1.25%, 800 mL) and cooled to 5 °C on an ice bath. Sodium nitrite (5g, 72 mmol) dissolved in water (150 mL) was added slowly while keeping the temperature of the reaction below 5 °C. After addition of the sodium nitrite the reaction was stirred for another 45 min at 5-10 °C until a clear solution was obtained. The reaction mixture was poured into hot (70-85 °C) water (1.5 L), charcoal added and the reaction mixture heated at reflux for 25 min. Filtration and extraction with ethyl acetate afforded 6.7g of the desired product as light brown crystals

Example 3
(intermediate)

2-Chloro-3-hydroxy-4-nitro-benzoic acid

To a solution of 2-chloro-5-hydroxybenzoic acid (6.5g, 38 mmol) in cold acetic acid (150 mL) was added concentrated nitric acid (2.7 mL, 38 mmol). After addition the reaction mixture was stirred for 30 min at room temperature then heated at 35 °C for 20 min. The reaction mixture was poured into ice and the product filtered off to give 1.5 g of the desired compound as yellow crystals.

Example 4
(intermediate)

4-Amino-6-chloro-3-hydroxybenzoic acid

2-Chloro-3-hydroxy-4-nitro-benzoic acid (2.2g, 10 mmol) dissolved in ethanol (120 mL) was reduced over Raney-Ni to give 1.7 g of black crystals.

Example 5**3'-Trifluoromethylphenyl-4-carboxy-5-chloro-2-hydroxyphenyl urea**

4-Amino-6-chloro-3-hydroxybenzoic acid (1.6g, 8.6 mmol) and 3-trifluoromethylphenyl isocyanate (1.2 mL, 9 mmol) were mixed in toluene (100 mL). The reaction was heated at reflux for 2 hr. The cooled reaction was filtered. The crude product was dissolved in ethanol at reflux and treated with activated charcoal. Subsequent re-crystallisation from ethyl acetate afforded the 1.2 g of the desired compound. M.p. 267-268 °C.

Example 6**3'-Trifluoromethylphenyl-2-amino-5-chlorophenyl urea**

3-Trifluoromethylphenyl-5-chloro-2-nitrophenyl urea (4.0g, 11 mmol) was dissolved in ethanol (200 mL). Raney-Ni (approx. 2 g) was added and the reaction hydrogenated for 4 hr at room temperature. Filtration and evaporation of the solvent afforded 3.2g of the desired compound as light pink crystals.

Example 7**3'-Trifluoromethylphenyl-5-chloro -2-methanesulfonylaminophenyl urea**

3'-Trifluoromethylphenyl-2-amino-5-chlorophenyl urea (0.5g, 1.5 mmol), methanesulphonylchloride (1.19 mL, 2.5 mmol), pyridine (0.4 mL, 5 mmol) and tetrahydrofuran (25 mL) were mixed and heated at reflux for 5 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The crude product was purified by column chromatography on silica gel using toluene/ethyl acetate (1:1) as eluent. 0.1 g of the desired material was obtained. M.p. 185-186 °C.

Example 8**3'-Trifluoromethylphenyl-2-carboxyphenyl urea Isopropyl ester**

To 3'-trifluoromethylphenyl-2-carboxyphenyl urea (3.24 g, 10 mmol) was added thionyl chloride (15 mL). After heating the reaction at 50 °C for 1 hr the excess thionyl chloride was evaporated. The residue was stirred up in diethyl ether and filtered off to give 2.9 g of the desired acid chloride. The acid chloride (1.5 g) was added to isopropanol (15 mL). The reaction was stirred at room temperature overnight. The solvent was evaporated and the residue re-crystallised from ethanol (96%, 20 mL) to give 0.65 g of the desired material. M.p. 137-138 °C.

Analogously were made:

3'-Trifluoromethylphenyl-2-carboxyphenyl urea methyl ester. M.p. 169-170 °C.

3'-Trifluoromethylphenyl-2-hydrazinocarbonylphenyl urea. M.p. 172-173 °C.

3'-Trifluoromethylphenyl-2-hydroxylaminocarbonylphenyl urea. M.p. 210-212 °C.

Example 9**2-(3'-Trifluoromethylbenzylcarboxamido)benzoic acid**

To 3-trifluoromethylphenylacetic acid (2.70 g, 13.2 mmol) in diethyl ether (100 mL) was added thionyl chloride (2 mL, 27 mmol). After heating at reflux for 1 hr the reaction mixture was evaporated to dryness. The residue was dissolved in diethyl ether and 2-aminobenzoic acid (1.85 g, 13.5 mmol) was added followed by triethylamine (5 mL). After stirring for 30 min water was added and the organic phase washed with 4 N hydrochloric acid. Re-crystallisation from aqueous ethanol gave 0.95 of the desired material. M.p. 162-164 °C.

Example 10
(intermediate)

2-methylsulfonamidocarbonylaniline

Lithium methanesulfonamidate (1.0 g, 10 mmol) and isatoic anhydride (1.63 g, (10 mmol) in dimethyl sulfoxide (5 mL) were heated at 80 °C for 30 min. The reaction was cooled down to room temperature and acidified with hydrogen chloride in diethyl ether. The ether was evaporated and water added. The precipitated oil was purified by column chromatography on silica gel eluting with ethyl acetate/methanol (95:5). The desired material was obtained in a yield of 0.52 g.

Analogously were made;

2-phenylsulfonamidocarbonylaniline

Example 11

3'-Trifluoromethylphenyl-4-carboxyphenyl urea

3'-Trifluoromethylphenyl isocyanate (1.7 mL, 10 mmol) and 4-aminobenzoic acid (1.37 g, 10 mmol) were stirred in dimethyl sulfoxide (20 mL) for 30 min. The reaction mixture was poured into water. The precipitate was filtered off and washed with water. The filter cake was stirred up in 4 N sodium hydroxide and filtered through celite. The filtrate was acidified and the precipitate filtered off. Washing with water and drying in the air afforded 3.0 g of the desired material. M.p. >300 °C.

Analogously were made:

3'-Trifluoromethylphenyl-2-carboxy-4-nitrophenyl urea. M.p. 185-186 °C.

3'-Trifluoromethylphenyl-2-carboxynapht-3-yl urea. M.p. 197-198 °C.

3'-Trifluoromethylphenyl-4-methoxy-2-carboxyphenyl urea. M.p. 175-176 °C.

3'-Methoxyphenyl-2-carboxyphenyl urea. M.p. 162-163 °C (dec.).

4'-Bromophenyl-2-carboxyphenyl urea. M.p. 153-154 °C (dec.).

3'-Nitrophenyl-2-carboxyphenyl urea. M.p. 190-191 °C (dec.).

2'-Methoxyphenyl-2-carboxyphenyl urea. M.p. 160-161 °C (dec.).

4'-Methoxyphenyl-2-carboxyphenyl urea. M.p. 175-176 °C (dec.).

1'-Naphthyl-2-carboxyphenyl urea.

2'-Trifluoromethylphenyl-2-carboxyphenyl urea. M.p. 172-163 °C (dec.).

4'-Methylphenylsulfonyl-2-carboxyphenyl urea. M.p. 166-168 °C (dec.).

Example 12

(intermediate)

Ethyl N-(2-bromoethyl)aminobenzoate

Dibromomethane (21.5 mL, 0.25 mol), ethyl-2-aminobenzoate (3.7 mL, 0.25 mmol) and triethylamine (4.2 mL, 30 mmol) were mixed in dimethylformamide (50 mL) and heated at 110°C for five hours. After cooling to room temperature the reaction was poured onto ice and extracted with diethyl ether. The organic solution was washed with water, dried over magnesium sulphate and evaporated to dryness. The residue was purified by column chromatography on silica gel using dichloromethane as eluent to give 3.3 g of the desired material.

Example 13

N'-(3-Trifluoromethylphenyl)-N-(2-ethyloxycarbonylphenyl)-1,2-diaminoethane

Ethyl N-(2-bromoethyl)aminobenzoate (3.3 g, 12 mmol), 3-aminobenzotrifluoride (1.5 mL, 12 mmol) and triethylamine (2 mL, 14 mmol) were mixed in dimethylformamide (25 mL). The reaction mixture was heated at 110°C for five hours. The cooled reaction mixture was poured into water and extracted with diethyl ether. Purification by column chromatography on silica gel using dichloromethane as eluent gave 1.6 g of the desired material.

Example 14**N-(3-Trifluoromethyl)phenyl-N'-(2-carboxy)phenylsulfamide**

A mixture of 3-acetamidobenzotrifluoride (3.0 g, 15 mmol) and 60% sodium hydride (0.6 g, 15 mmol) was stirred in toluene overnight at 60 °C. A solution of thionyl chloride (1.2 mL, 15 mmol) in petroleum ether (10 mL) was added to the mixture while keeping the temperature below 8 °C. After stirring at 6-8 °C for 2 hr the reaction was filtered and the filtrate evaporated to dryness. The residue was dissolved in diethyl ether (50 mL) and 2-aminobenzoic acid (2.0 g, 15 mmol) was added. After heating the reaction at reflux for 13 hr the solvent was evaporated. The residue was heated to reflux in 2N sodium hydroxide. The reaction was acidified and the precipitate filtered off. Purification by column chromatography on silica gel using ethyl acetate as eluent gave the desired compound. M.p. 162-163 °C.

Example 15**3'-Trifluoromethylbenzyl-2-carboxyphenyl urea**

To a solution of di-tert-butyl dicarbonate (0.68 g, 3.13 mmol) in methylene chloride (25 mL) were added dimethylaminopyridine (36 mg, 0.3 mmol) and 3-trifluoromethylbenzylamine (0.43 mL, 3 mmol). After stirring for 20 min at room temperature 2-aminobenzoic acid (0.43 g, 3.13 mmol) was added. The reaction was heated at reflux overnight. The solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with 1 M hydrochloric acid and water. The solvent was evaporated and the residue suspended in water. 4 N Sodium hydroxide (1.25 mL, 5 mmol) was added. The resulting suspension was washed with diethyl ether and acidified with 4 N hydrochloric acid. The precipitate was filtered off and washed with water. Re crystallisation from aqueous ethanol gave 80 mg of the desired material. M.p. 176-178 °C.

The compound 3'-trifluoromethyl-4-phenylphenyl-2-carboxyphenyl urea, M.p. 191-192 °C (dec.), was prepared analogously.

Example 16
(intermediate)

2-Amino-4-phenylbenzonitrile

A mixture of 2-amino-5-bromobenzonitrile (1.0 g, 5 mmol), phenylboronic acid (0.92 g, 7.5 mmol), tetrakis(triphenylphosphine)palladium (50 mg) and potassium carbonate (3.5 g, 25 mmol) in dimethoxyethane/water 2:1 (60 mL) was heated at reflux for 4 hours. After cooling to room temperature the reaction was diluted with water and extracted with ethyl acetate. The organic phase was dried and solvent evaporated. Trituration with petroleum ether gave 0.89 g of the desired compound.

Example 17

2-(3'-Trifluoromethylphenyloxycarbonylamino)benzoic acid

To a solution of 1.9 M phosgene in toluene (6.3 mL, 12 mmol) was added 3-hydroxybenzotrifluoride (1.62 g, 10 mmol) in toluene (30 mL) followed by triethyl amine (1.7 mL, 12 mmol) in toluene. After stirring for 15 min 2-aminobenzoic acid (1.37 g, 10 mmol) was added. The reaction was stirred overnight at room temperature. The precipitate was filtered off and washed successively with water, toluene and petroleum ether to give 1.0 g of the title compound. M.p. 150-152 °C.

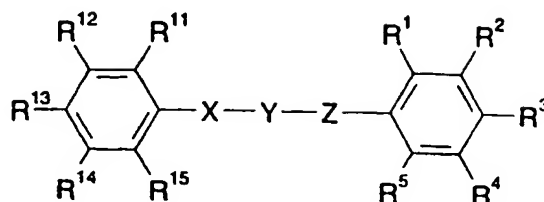
Example 18

3'-Trifluoromethylphenyl-5-chloro-2-aminophenyl urea

To a solution of 3'-trifluoromethylphenyl-5-chloro-2-nitrophenyl urea (1.0 g, 2.8 mmol) in ethanol (50 mL) was added Raney-nickel. After stirring overnight the reaction was filtered and the filtrate evaporated to dryness to give 0.8 g pink crystals. M.p. 308 °C.

CLAIMS:

1. A compound having the formula



or a pharmaceutically acceptable salt thereof

wherein

one of R^1 , R^2 and R^3 is a non-cyclic acidic group having a pKa value below 8 or a group which is in vivo convertible to such a group;

R^4 , R^5 and the other two of the substituents R^1 , R^2 and R^3 are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl and heteroaryl groups may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or R^3 and R^4 or R^4 and R^5 together form a fused 4 to 7 membered carboxycyclic ring which may be unsaturated, or partially or fully saturated, while the other substituents R^1 , R^2 , R^3 , R^4 and R^5 is as defined above;

Y is $-CO-$, $-CS-$, $-SO_2-$, or $-C(=N-R^6)-$, wherein R^6 is hydrogen, alkyl, or cyano;

X is $-NH-$, $-CH_2-NH-$, or $-SO_2-NH-$;

Z is NR^6 , O, $-CH=CH-$, $-C\equiv C-$, $-N=CH-$, or $-CH=N-$; wherein R^6 is hydrogen, or alkyl;

R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; $-NHSO_2-R^7$, $-COOR^7$, $-SO_2N(R^7)_2$, $-SO_2OR^7$ and

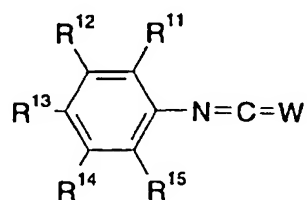
-CO-R⁷, wherein R⁷ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl or aralkyl; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl and heteroaryl groups may be substituted one or more times with substituents selected from alkyl, cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R¹¹ and R¹², R¹² and R¹³, R¹³ and R¹⁴ or R¹⁴ and R¹⁵ together form a fused 4 to 7 membered carboxylic ring which may be unsaturated, or partially or fully saturated, while the other substituents R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above.

2. A compound according to claim 1 wherein one of R¹, R² and R³ is NH₂, -COOR⁹, -CH₂COOR⁹, -CONH₂, -NHSO₂-R⁹, -SO₂N(R⁹)₂, -SO₂OR⁹, -PO₃H₂, -PO₃RH, -PO₂NH₂, -CONHOH, -CONHCN, -CONH₂SO₂R⁹ and -CONHNH₂, wherein R⁹ is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl or aralkyl, and the other of R¹, R² and R³ is as defined in claim 1.
3. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claims 1 to 2 or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier or diluent.
4. The use of a compound according to claims 1 to 2 for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels.
5. The use of a compound according to claims 1 to 2 for the preparation of a medicament for the treatment of sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic), glaucoma, allergic or inflammatory conditions and ulcers.
6. A method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to a living animal body in need thereof a therapeutically effective amount of a compound according to claim 1.

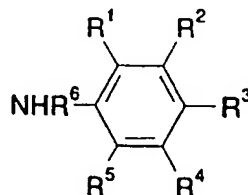
7. A method for the treatment of a disorder or disease of a living animal body which disorder or disease is sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic), glaucoma, allergic or inflammatory conditions and ulcers comprising administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound according to claim 1.

8. A method for the preparation of a compound of claim 1, comprising:

a) reacting a compound having the formula

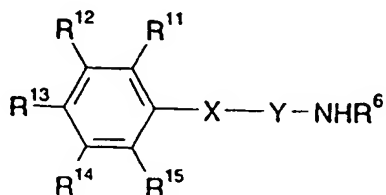


wherein W is O, or S and R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above, with a compound having the formula

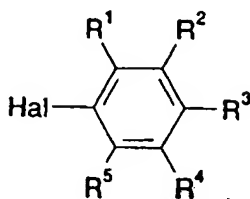


wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 is as defined above, or

b) reacting a compound having the formula



wherein X, Y, R⁶, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above, with a compound having the formula



wherein Hal is halogen and R¹, R², R³, R⁴ and R⁵ is as defined above,

whereafter the compound obtained is optionally converted to another compound of the invention and/or a pharmaceutically acceptable salt thereof is formed using conventional methods.

9. The use of blockers of chloride channels of erythrocytes for the treatment of sickle cell anaemia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/02723

A. CLASSIFICATION AND SUBJECT MATTER
IPC 6 C07C275/42 C07C311/39 C07C311/51 C07C335/22 C07C275/40
C07C311/08 C07C311/60 C07C271/58 A61K31/19 A61K31/17
A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 22807 A (NEUROSEARCH A/S, DEN.) 13 October 1994 see page 29, line 3, 11-12, 15-18, 20 see example 8; page 33, line 8, 13 see page 34, line 17, 19, 24, 30-31, page 35, line 1-2, 4-5 see claims 1,3,5,11 ---	1-3,5,7,8
X	DE 29 28 485 A (BAYER AG) 29 January 1981 see examples 4, 44, 57, 67, 69, 70, 72, 112, 114, 119-121, 131 ---	1,2
X	US 4 468 380 A (O'DOHERTY GEORGE O P ET AL) 28 August 1984 see examples 1-11 ---	1,2
X	US 3 798 268 A (TWEIT R) 19 March 1974 see claims; examples ---	1,2,8
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

22 August 1997

Date of mailing of the international search report

29.08.97

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/02723

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 784 564 A (ROHR W ET AL) 8 January 1974 see column 3, line 3 - line 13 ---	1,2
X	GB 1 139 343 A (AGRIPAT) 8 January 1969 see table I, examples 13-15, 17, 19, 43, 44 see table III, examples 26, 30-34 see claims 1,11,35 ---	1-3,8
X	GB 828 231 A (J. R. GEIGY AG) 17 February 1960 see claims; examples ---	1,2,8
X	US 2 722 544 A (H. M. FEUERTHALEN) 1 November 1955 see claims; examples ---	1,2,8
X	GB 1 055 786 A (IMPERIAL CHEMICAL INDUSTRIES) 18 January 1967 see claims; examples ---	1,2,8
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 22, 1993, WASHINGTON US, pages 3397-3408, XP002038034 R. W. CARLING ET AL.: "3-Nitro-3,4-dihydro-2(1H)-quinolones. Excitatory amino acid antagonists acting at glycine-site NMDA and (RS)-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors" see intermediate 37 for compound 17, table III see page 3407, left-hand column, line 17 - line 21 ---	1,2
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Intern. Appl. No.

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C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	<p>--- CHEMICAL ABSTRACTS, vol. 107, no. 11, 14 September 1987 Columbus, Ohio, US; abstract no. 89293, WANGEMANN, P. ET AL: "Chloride - channel blockers in the thick ascending limb of the loop of Henle. Structure-activity relationship" XP002038036 cited in the application see abstract & PFLUEGERS ARCH. (1986), 407 (SUPPL. 2), S128-S141,</p>	4,6
A	<p>--- US 4 994 493 A (GREGER RAINER ET AL) 19 February 1991 cited in the application see claims</p>	5,7
A	<p>--- WO 96 08242 A (CHILDRENS MEDICAL CENTER) 21 March 1996 see claims</p> <p>-----</p>	5,7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/02723

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6 and 7
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see next sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The vast number of theoretically conceivable compounds resulting from the combination of all claimed substituents precludes a comprehensive search for all compounds according to claim 1. For economic reasons the search has been limited to compounds where at least one of the substituents R11-15 is a CF₃-group.

Despite the above limitation the search revealed too many relevant documents and/or compounds, so that the search report shall not be considered complete. The citations in the search report are only a arbitrary selection of novelty destroying compounds/documents.

INTERNATIONAL SEARCH REPORT

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Internat J Application No

PCT/EP 97/02723

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